

TMS of the right angular gyrus modulates priming of pop-out in visual search: combined TMS-ERP evidence

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Taylor PC, Muggleton NG, Kalla R, Walsh V, Eimer M. TMS of the right angular gyrus modulates priming of pop-out in visual search: combined TMS-ERP evidence. *J Neurophysiol* 106: 3001–3009, 2011. First published August 31, 2011; doi:10.1152/jn.00121.2011.—During priming of pop-out, performance at discriminating a pop-out feature target in visual search is affected by whether the target on the previous trial was defined by the same feature as on the upcoming trial. Recent studies suggest that priming of pop-out relies on attentional processes. With the use of simultaneous, combined transcranial magnetic stimulation and event-related potential recording (TMS-ERP), we tested for any critical role of the right angular gyrus (rANG) and left and right frontal eye fields (FEFs)—key attentional sites—in modulating both performance and the ERPs evoked by such visual events. Intertrial TMS trains were applied while participants discriminated the orientation of a color pop-out element in a visual search array. rANG TMS disrupted priming of pop-out, reducing reaction time costs on switch trials and speeding responses when the color of the pop-out target switched. rANG TMS caused a negativity in the ERP elicited in response to the visual stimulus array, starting 210 ms after stimulus onset. Both behavioral and ERP effects were apparent only after rANG TMS, on switch trials, and when the target in the visual search array was presented in the left visual field, with no effects after left or right FEF TMS. These results provide evidence for an attentional reorienting mechanism, which originates in the rANG and is modulated by the implicit memory of the previous trial. The rANG plays a causal role on switch trials during priming of pop-out by interacting with visual processing, particularly in the ipsilateral hemisphere representing the contralateral hemifield.

EEG; posterior parietal cortex; frontal eye fields

VISUAL SEARCH PERFORMANCE is strongly affected by task history. When participants are instructed to detect and discriminate an odd-one-out color singleton in an array (“pop-out” search), reaction times (RTs) are faster if, say, a red target amongst green distractors is presented on two consecutive trials (a repeat trial) rather than when there is a role-reversal of target and distracter, such that on the subsequent trial, the target color switches to green, and the distracters are all red (“switch” trial) (Maljkovic and Nakayama 1994). The behavioral “priming of pop-out” effect has been suggested to depend on a memory trace, which holds representations storing color-based target and distractor properties of the preceding trial across the intertrial interval, potentially interfering with performance on the next trial (Maljkovic and Nakayama 1994). Priming of pop-out is implicit, and so may confer a behavioral advantage

by biasing attentional selection on the upcoming trial toward stimuli that have been functionally important recently, without requiring more explicit control. There is currently an active controversy about the locus of the priming effect, i.e., which stages of processing are modulated by this implicit memory trace. The “attentional” account of priming of pop-out postulates that attentional processes during the intertrial interval are sensitive to and are modulated by the implicit memory trace (Chun and Nakayama 2000). Alternatively, intertrial effects during priming of pop-out might be located at postattentional processing stages, such as response selection (Theeuwes et al. 2006).

A frontoparietal network of areas has been suggested from imaging studies to form an attentional control network (Corbetta and Shulman 2002; Grosbras et al. 2005; Nobre 2001). For example, transcranial magnetic stimulation (TMS) has been used to show that the right angular gyrus (rANG) (Ellison et al. 2003) and frontal eye field (FEF) (Muggleton et al. 2003) are critical for conjunction visual search. However, TMS does not affect pop-out performance when the target color is simply repeated on every trial. Furthermore, rANG TMS disrupts performance at a wide range of tasks, interfering with performance when the to-be-attended target needs to be updated, e.g., if the target switches from trial to trial (reviewed in Rushworth and Taylor 2006). If the attentional account of priming is correct, then these areas may also be sensitive to task history and be modulated by implicit memory during the intertrial interval, even though these areas are not critical for priming of pop-out on repeat trials. A functional MRI (fMRI) study found that intertrial priming of feature pop-out is correlated with changes of activity within the posterior parietal cortical (PPC), FEFs and medial frontal cortex (Kristjansson et al. 2007). Some recent TMS studies have also investigated whether TMS of these attentional control areas also affects priming. For example, intertrial left FEF TMS disrupts priming for spatial position when participants are manually responding as to the direction in which the pop-out target is moving (Campana et al. 2007). By contrast, left FEF TMS at stimulus onset (and not between trials) disrupts the spatial priming of saccades to odd-colored targets (O’Shea et al. 2007). Left FEF intertrial TMS affects color priming when the task is to manually respond to the spatial position of the target (Muggleton et al. 2009).

It remains unclear which neural areas play a critical role in the processes implemented by the classical behavioral priming of pop-out tasks, in which participants manually respond to the shape of a color pop-out. Note that this “compound” task

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dissociates between the feature driving pop-out (color) and that used for response selection (shape). The effects of TMS may be highly sensitive to the timing of the stimulation, the feature determining the pop-out, the feature specifying the response, and the effector. Given the substantial evidence implicating the rANG in attentional control, the fact that some previous studies have reported evidence implicating the FEF in priming of pop-out may be due to the specific task used. In the current study, we extend such work by using a compound task identical to that used in the classic studies of priming of pop-out (Maljkovic and Nakayama 1994). This task requires focal attention to report the form of a static color singleton and involves manual responses. It is currently not known which areas may play more or less of a causal role in the intertrial period of this pop-out task, and so here, we directly contrasted the effects of intertrial TMS to key regions previously implicated in attentional control and to priming of pop-out by TMS. These included the left and right FEFs and the rANG. Areas that have been stimulated during visual search without effect, such as the angular gyrus of the left hemisphere (Ashbridge et al. 1997; Rushworth et al. 2001), were not stimulated in the present study.

In addition, this study probed the potential involvement of the FEF or rANG in modulations of visual processing associated with priming of pop-out by combining TMS online with event-related potential (ERP). Combined TMS-ERP allows testing whether and when activity in the stimulated area is critical for the task-specific modulation of activity in other areas and with high temporal resolution (Driver et al. 2009; Miniussi and Thut 2009; Taylor et al. 2008). Here, we used combined TMS-ERP to study whether rANG or left or right FEF stimulation affects the pattern of behavioral priming of pop-out effects and whether any of these areas are necessary for modulations of visual processing, which are induced by intertrial priming. Any specific effects over visual areas would again be consistent with the attentional account, as opposed to an effect on response selection mechanisms.

A further issue within priming of pop-out concerns differences between the processes occurring on repeat and switch trials. If TMS disrupted the memory trace itself and not attentional processes, this should attenuate or eliminate any benefits on repeat trials. In contrast, TMS-induced effects on switch trials would be more in line with the attentional account and with previous work implicating the FEFs and rANG in reorienting, switching, or updating. Because attentional settings do not need to be changed on repeat trials, effects of stimulating these areas should be limited to switch trials. This

would also be in line with previous work, where TMS of the FEFs or rANG had no effect on pop-out search where the target was kept constant, and so effectively, every trial was a repeat trial (Ashbridge et al. 1997; Muggleton et al. 2003).

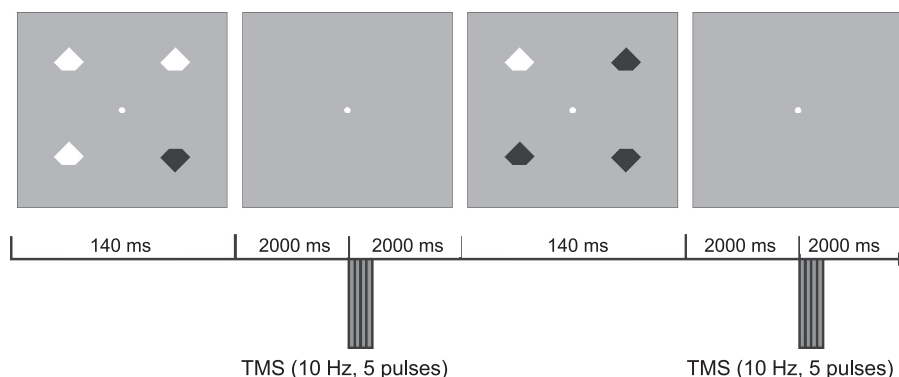
MATERIALS AND METHODS

Data from 12 participants (mean age 22; range 19–30; six women) were analyzed following an initial screening (see below). All participants were right handed with normal or corrected-to-normal vision and gave written, informed consent. The experimental protocol was approved by the Ethics Committee of the School of Psychology at Birkbeck College (London, UK).

Figure 1 shows the task. A fixation point was presented throughout each experimental block. On each trial, a stimulus array, consisting of four pentagons, was presented for 140 ms. Intertrial interval was 4,000 ms, and trial duration was fixed, independent of RT. The pentagons had a cut either at the top or the bottom, and one of the pentagons was always a different color from the other three, either red amongst green or vice versa. The participants' task was to identify the location of the cut of the colored singleton pentagon and to respond as quickly and accurately as possible by pressing "h" with the left index finger if the cut was at the top and "n" with the right index finger if the cut was at the bottom. This ensured that there was no systematic relation between the stimulated hemisphere and the responding hand. Accuracy was high (mean 95%; see below), meaning no instruction was necessary about what to do if unsure and ensuring maximal power for the analysis of ERP data, which only examined correct trials. The location, color, and cut location of the target and nontarget pentagons were all randomized, such that in one-half of all trials, target and nontarget colors were repeated relative to the preceding trial (repeat trials), whereas in the other half, target and nontarget colors were swapped (switch trials). Each pentagon was 2° wide and 1.5° tall, positioned at the outer corners of a virtual rectangle, 5.2° wide and 2.6° tall. The red and green stimuli had R,G,B values of 180,0,0 (red) and 0,150,0 (green) and were presented against a gray background [International Commission on Illumination (Vienna, Austria) values (x,y): red, 0.602,0.342; green: 0.287,0.545; gray: 0.287,0.303] on a liquid crystal display computer monitor at 1,024 × 768 pixels resolution with a refresh rate of 75 Hz (monitor model SDM-S73, made by Sony, Tokyo). Participants sat with their head in a chinrest, 57 cm from the monitor. Stimuli, responses, and TMS/ERP triggering were generated by E-Prime software (Psychology Software Tools, Sharpsburg, PA).

Prior to the experimental blocks, participants were tested on three successive practice blocks of 48 trials. Four participants failed to show the standard priming of pop-out effect (defined as a RT benefit for repeat, relative to switch trials of at least 20 ms) in these blocks, and these were not tested in the main experiment. A 20-ms cutoff was used as the arbitrary cutoff value, because the normal range of priming of pop-out effects has been described previously as falling within the range of 20–50 ms (Maljkovic and Nakayama 1996). Following

Fig. 1. Task. An example of 2 successive trials. On each trial, the task was to respond manually according to the form of the color singleton. Transcranial magnetic stimulation (TMS) was applied in separate blocks to the right angular gyrus (rANG) or the left or right frontal eye fields (FEFs), starting 2,000 ms into the intertrial interval (10 Hz, 5 pulses). The right-hand trial is an example of a switch trial (the color of the singleton target has switched on successive trials), with the target presented in the left visual field. Note that stimuli were actually colored, not grayscale as shown.



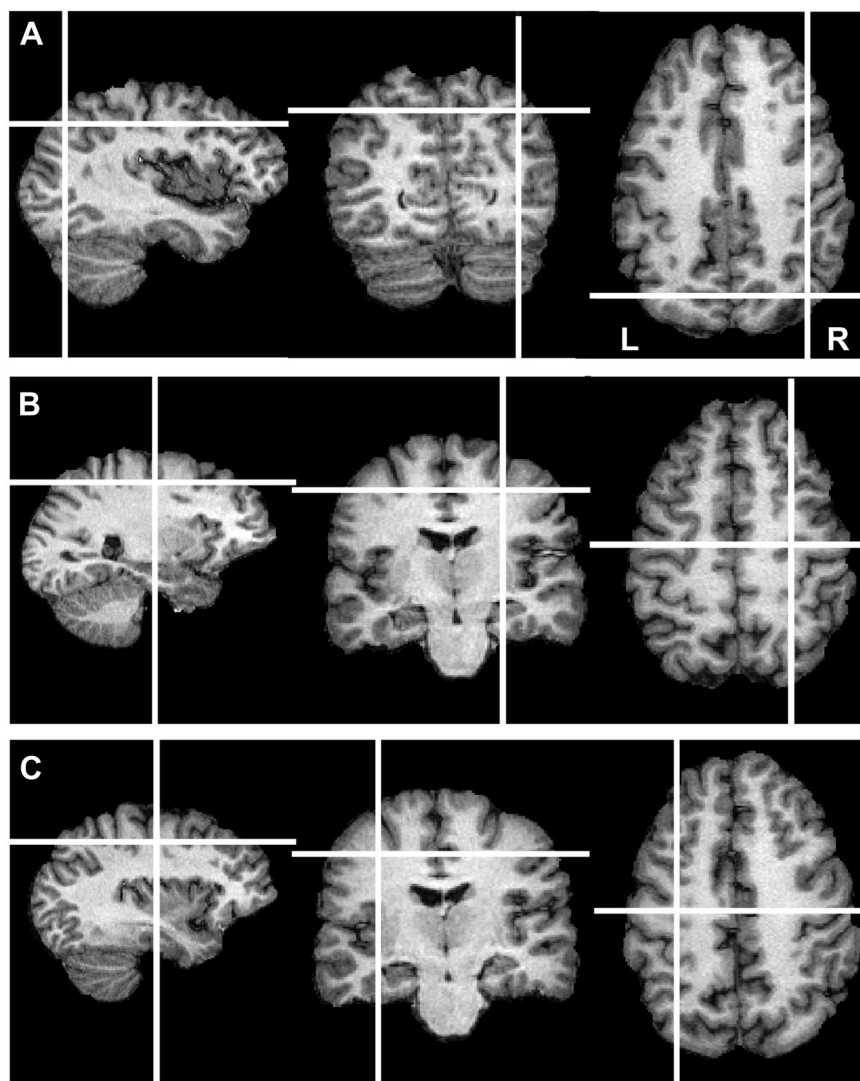


Fig. 2. TMS sites. All TMS sites were localized on each individual participant's MRI scan using coordinates from previous studies and targeted using stereotactic registration. This figure shows 1 example participant for the 3 sites. A: rANG; B: right FEFs; C: left FEFs.

practice, stimuli were presented in blocks of 96 trials. The duration of the brief break halfway through the block was participant controlled. Each block lasted ~7 min, including break. Blocks were run either without TMS (no-TMS) or with TMS over the rANG or the left or right FEFs, resulting in four TMS conditions performed in the same session. TMS was performed in blocks to prevent participants from being distracted by anticipating whether the trial might be a TMS trial. Participants performed two blocks for each TMS condition (eight blocks in total). Block order was counterbalanced across participants pseudorandomly: participants performed eight blocks subdivided into two groups of four, and each condition was performed once within each group with sequences of four generated randomly. On TMS trials, TMS was presented halfway through the intertrial interval, i.e., 2,000 ms before a search array was presented on the next trial. TMS was always applied at the same time during the fixed intertrial interval to ensure that the time from the TMS to the next upcoming stimulus was always the same. TMS and ERP recordings were performed simultaneously on the same subjects.

TMS sites and parameters. TMS parameters were selected so as to be as similar as possible to the parameters used in similar, previous studies, exploiting successful protocols that demonstrated critical roles in attentional tasks for the rANG (Muggleton et al. 2006) and FEF (Muggleton et al. 2009). TMS was applied at 10 Hz in trains of five pulses using figure-eight flat coils (Magstim, Whitland, Wales). The train of TMS was therefore 400-ms long (five pulses at 10 Hz).

The average interburst interval was kept fixed at 4,140 ms (the same as the trial length). Importantly, this TMS protocol does not produce lasting offline effects, which may occur only after long trains of many dozens of pulses without such breaks between trains (Rossi et al. 2009). For rANG TMS, a 70-mm diameter coil was placed with the coil end pointing downward, with the center of the coil (maximal stimulation) centred over Montreal Neurological Institute (MNI) coordinates (x,y,z): 42, -58, 52. We chose these coordinates from a previous study, which found that TMS at this position disrupted conjunction visual search (Gobel et al. 2001; see also Muggleton et al. 2006). For FEF TMS, a 50-mm diameter coil was held with the handle pointing backwards, centred over MNI coordinates (x,y,z): -32, -2, 46 (left FEF); 31, -2, 47 (right FEF), according to a meta-analysis of imaging studies of the FEF during eye movements (Paus 1996) and where TMS has also affected priming of pop-out in a different task (as in Muggleton et al. 2009). Note that these exact combinations of coil type, orientation, and position were selected because they have been shown to disrupt priming in those previous studies. Additionally, the use of a 50-mm coil for FEF stimulation helps to reduce EEG artifacts produced through eye blinks or mechanical contact between the coil and EEG electrodes. MNI coordinates were converted into the space of each individual participant's scan using fMRI of the brain's linear image registration tool (FLIRT) (Jenkinson et al. 2002). TMS sites were labeled on each participant's structural magnetic resonance image taken with a 3T scanner (Fig. 2), and then targeted using

infrared stereotactic registration (Brainsight, Rogue Research, Montreal, Quebec, Canada). A standard stimulation intensity of 65% maximal stimulator output of the Magstim Rapid2 machine (Magstim) was used throughout, thereby matching the previous TMS studies of priming and also controlling for the effect of TMS on the EEG across conditions.

Electrophysiological recording and data analysis. EEG was direct current (DC) recorded continuously at 1,000 Hz with a TMS-compatible ERP amplifier capable of recording a veridical EEG within 40 ms of a TMS pulse (BrainAmp DC, Brain Products, Germany). EEG was recorded with the least possible filtering (DC; high cutoff at 450 Hz; no notch filter) from a whole-head montage of custom-built Ag-AgCl electrodes (each with a built-in 5-kOhm resistor) at positions CP5, CP6, Cz, F7, F8, FC5, FC6, FPz, Fz, P3, P7, P8, PO7, PO8, Pz, T7, and T8. Horizontal electrooculography (HEOG) was recorded from the left and right temples. The ground electrode was at AFz with the active reference on the left earlobe (Luck 2005). Electrode impedance was kept below 10 k Ω . Data were re-referenced to the average of the left and right earlobes, and a HEOG signal was formed by subtracting the right HEOG from the left HEOG. Data were then epoched to form 600-ms segments containing the whole trial and starting 100 ms before onset of the visual search array. Filtering used a notch 50-Hz filter and then a Butterworth zero-phase filter with low cutoff set to 0.01 Hz (lowest effective filtering at 1.67 Hz) and high cutoff of 40 Hz (12 dB/octave). Participants were instructed to only blink or move their eyes during the intertrial interval. Baseline correction used the first possible period of clean ERP data—the 100 ms before onset of the visual stimulus, which was the event of interest in this study. Automated ERP artifact rejection removed trials with eye movements by eliminating trials where the HEOG signal exceeded ± 30 μ V. Blinks were removed by deleting trials if the signal at FPz exceeded ± 60 μ V, and other movement-related artifacts were removed by eliminating any trials where the signal from any electrode exceeded ± 80 μ V. A minimum criterion of 30 trials/condition was set, which ensures a high signal-to-noise ratio of ERP averages (Regan 1989). Data from a further 10 tested participants failed to meet this strict criterion, and these participants were therefore excluded from all analyses. This meant that from the initial pool of 26 participants, four were rejected during initial behavioral screening, and 10 were rejected during ERP analysis, leaving 12 participants. To correct for multiple comparisons, the critical α level for post hoc *t*-tests was adjusted according to the Bonferroni correction throughout.

RESULTS

Behavioral. We applied an ANOVA, testing the factors priming (repeat, switch trials), visual field (left, right), and TMS condition (no-TMS, rANG, left FEF, right FEF). As expected from participant training and screening, RTs were longer on switch relative to repeat trials [500 vs. 448 ms; priming effect: $F(1,11) = 139.4$, $P < 0.001$]. An interaction between priming and visual field [$F(1,11) = 11.8$, $P < 0.01$] indicated that this priming of pop-out effect was generally more pronounced for targets in the left visual field. No three-way interaction was evident when considering all data from all four TMS conditions. However, a post hoc comparison showed that compared with no-TMS trials, only rANG TMS affected performance: with rANG TMS, a reduction in the size of the priming effect was observed, and this effect was specific to trials where targets were presented in the left visual field (i.e., contralateral to the stimulated hemisphere; see Fig. 3). Further analyses revealed that this reduction in the magnitude of priming of pop-out for targets in the contralateral hemifield was produced by a specific TMS-induced effect on switch trials, where rANG TMS facilitated performance: RTs on left

visual-field switch trials were faster when following rANG TMS than on no-TMS trials [496 vs. 516 ms; $t(11) = 2.5$, $P < 0.05$]. RTs on these left visual-field switch trials were also faster after rANG TMS than on trials after left FEF TMS [$t(11) = 2.2$, $P < 0.05$] and marginally so, compared with right FEF TMS trials [$t(11) = 1.9$, $P = 0.08$], all shown in Fig. 3. Thus performance after rANG TMS was different, not only from no-TMS but also from FEF TMS. Note that rANG TMS facilitated performance, reducing RTs. There were no differences in RTs on repeat trials and/or when the target was presented in the right visual field and/or with TMS of either left or right FEF (all $P \geq 0.3$).

Accuracy was generally very high (mean 95%), with slightly better performance on repeat than switch trials [97% vs. 93%; $F(1,11) = 30.6$, $P < 0.001$] and no other effects or interactions.

ERP. The visual search array elicited ERPs, which had the greatest amplitude over the lateral visual electrodes PO7 (left hemisphere) and PO8 (right hemisphere), which were therefore selected for further analysis. To identify electrophysiological correlates of the effects of rANG TMS on behavioral priming of pop-out effects, ERPs, in response to these search arrays, were compared as a function of TMS site, target hemifield, and priming condition. Fig. 4 shows lateral occipital ERPs for repeat and switch trials with targets in the left or right hemifield, separately for trials with rANG TMS and no-TMS trials. A differential effect of TMS on ERP amplitudes was observed only for left visual-field switch trials, that is, exactly for those trials where rANG TMS was found to modulate the magnitude of behavioral priming of pop-out. On these trials, rANG TMS resulted in an enhanced negativity of occipital ERPs relative to the no-TMS condition, which started ~ 210 ms after search-array onset (Figs. 4 and 5). In contrast, no such differential ERP modulation was observed for repeat trials, or switch trials where targets were presented in the right visual field.

Statistical analyses based on ERP mean amplitudes obtained at PO7 and PO8 substantiated these observations. We investigated the onset and offset of this effect by systematically averaging the amplitude of the ERP for each condition across 10-ms time bins for the entire epoch, from 0 ms to 400 ms after visual stimulus onset. Effects of TMS on priming were only taken as significant if there was an interaction involving TMS and priming for three successive time bins (for similar analyses, see Nobre et al. 2000; Taylor et al. 2007a, b) and if this was supported by pair-wise *t*-tests (testing for effects of TMS separately for each condition) for the same successive time bins (i.e., 30 ms minimum), in addition to multiple comparison correction for 40 successive *t*-tests from 0 ms to 400 ms (adjusted *P* value of $0.05/40 = 0.00125$). This conservative approach showed that the only effect occurred when comparing no-TMS and rANG TMS conditions and between 210 ms and 240 ms after visual stimulus onset, driven by an effect of TMS, present only at right hemisphere electrode PO8 and only for left visual-field switch trials [$t(11) \leq 4.3$, $P < 0.01$]. There were no effects earlier or later in the epoch nor any effects throughout the epoch for the comparisons of no-TMS with left FEF TMS or with right FEF TMS. With the use of the same systematic, 10-ms time-bin approach and multiple comparison correction, we also found that there were no main effects of priming within the no-TMS condition or within any TMS condition.

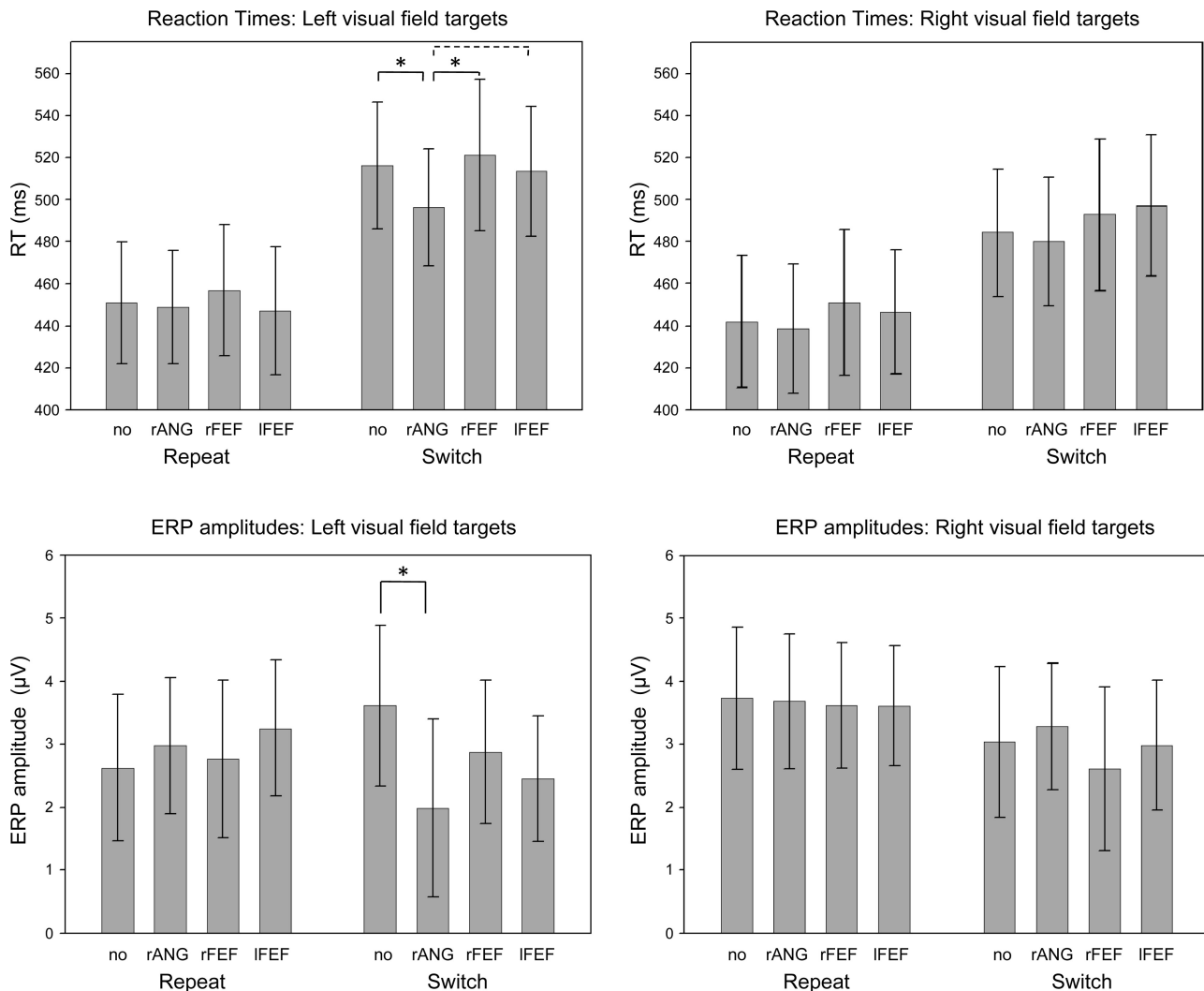


Fig. 3. Effect of TMS. rANG TMS had specific effects on the same trial type on both behavior [reaction time (RT); top left] and the event-related potential recording (ERP; bottom left). Only rANG TMS affected the behavior or the ERP compared with trials without TMS (no-TMS), and this was specific to switch trials. By contrast, there was no effect of TMS of the other sites. On the left, data are shown from trials where the target was presented in the left visual field (IFEF); there were no effects when the target was in the right visual field (rFEF), either on behavior (top right) or the ERP (bottom right). Behavioral data show the raw RTs. ERP data shown are the mean amplitudes between 210 ms and 300 ms after visual stimulus onset at right hemisphere electrode PO8. Error bars show SE. Asterisks show significant differences. Dashed line shows a trend.

To check that this result was not specific to the precise time window used in analysis, the high specificity of the effect to this 210- to 240-ms period was tested further by an analysis using successive, 30-ms time bins (Bonferroni corrected). This confirmed that the effect was uniquely apparent in this 210- to 240-ms window, left visual field, right cerebral hemisphere, switch condition, and TMS site [$t(11) = 5.86, P < 0.001$]. The previous analyses indicated that rANG TMS only affected the ipsilateral right visual cortex electrode PO8 and not the left electrode PO7. However, visual inspection of the ERP waveforms (Fig. 4) suggested that a weak but temporally extended effect might be present over the left hemisphere. To optimize capturing such an effect, if present, a more sensitive but less temporally specific analysis was performed on mean amplitudes obtained for electrodes PO7 and PO8 for each condition from each participant in the 210- to 300-ms interval after search-array onset; this revealed a weak and only marginally significant effect at PO7. When ERPs obtained in the no-TMS and rANG TMS conditions were analyzed together, a signifi-

cant interaction between TMS site, priming, and target hemifield [$F(2,22) = 4.7, P = 0.05$] was obtained. Follow-up analyses conducted separately for each of the eight combinations of priming, target hemifield, and hemisphere, shown in Fig. 4, and corrected for multiple comparisons confirmed significant ERP amplitude differences between the rANG and no-TMS conditions at right-hemisphere electrode PO8 [$t(11) = 4.4, P < 0.01$] for left visual-field switch trials, with only a marginally significant effect at left-hemisphere electrode PO7 [$t(11) = 2.8, P < 0.05$]. In contrast, no such TMS-induced ERP modulations were observed for repeat trials, or switch trials where targets were presented on the right side (all $P \geq 0.11$; Fig. 3). Two analogous analyses, which contrasted ERPs in the no-TMS condition with ERPs obtained in blocks where TMS was applied to the left or right FEFs, found no interaction between TMS site, priming, and target hemifield [both $F(2,22) < 0.2$], thus demonstrating that the TMS-induced modulations of ERPs for left visual-field switch trials shown in Fig. 3 were specific to rANG TMS. In addition, even a direct comparison revealed no

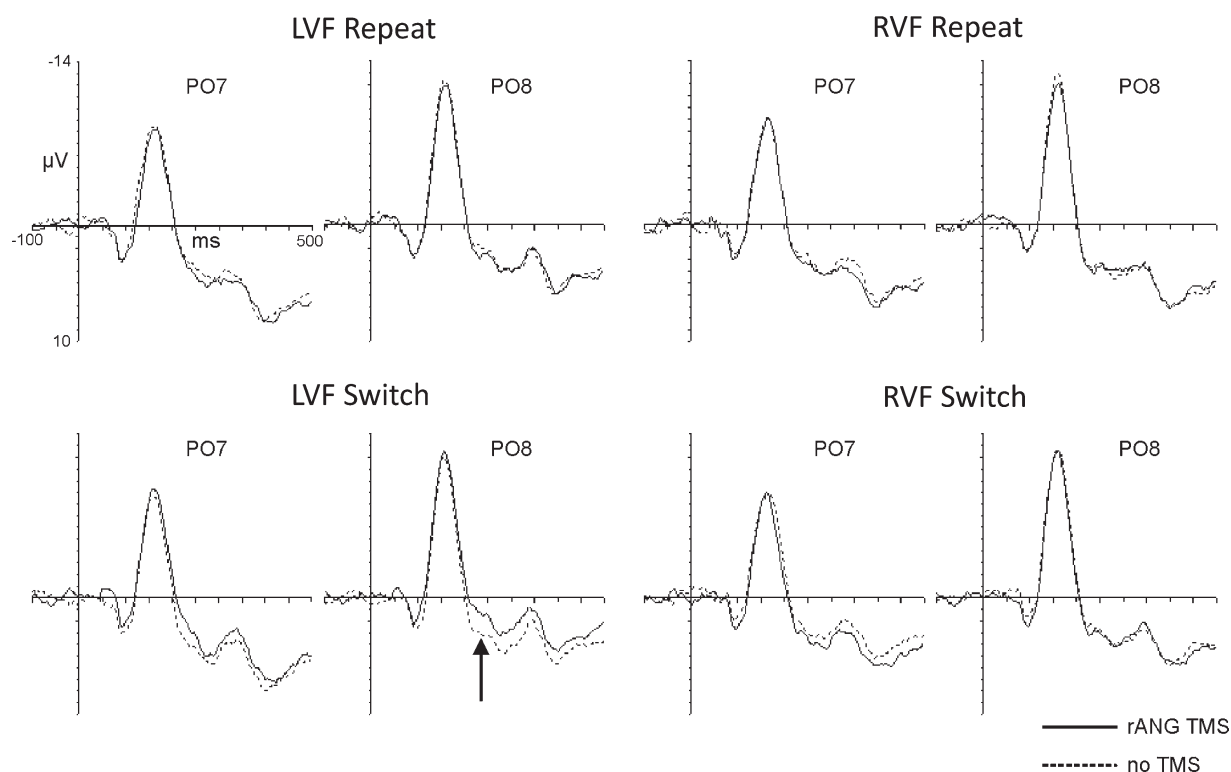


Fig. 4. Effect of rANG TMS on the ERP. rANG TMS only affected visual processing on switch trials and when the target was presented in the left visual field (LVF). This effect was apparent as a negative (upward) deflection after rANG TMS (thick line) compared with no-TMS (dashed line), starting at 210 ms (shown with black arrow). RVF, right visual field.

effects of TMS of either left or right FEFs on the ERP on left visual-field switch trials (all $P \geq 0.12$).

DISCUSSION

rANG TMS modulated the normal pattern of both behavior and neural activity during priming of pop-out visual search.

Both effects showed exactly the same specificity (Fig. 3): both were observed only on switch trials, i.e., trials where the color of the pop-out stimulus had switched from that on the previous trial, and both were present only on those switch trials where the target in the array was presented in the left visual field, contralateral to the stimulated (right) hemisphere. Relative to

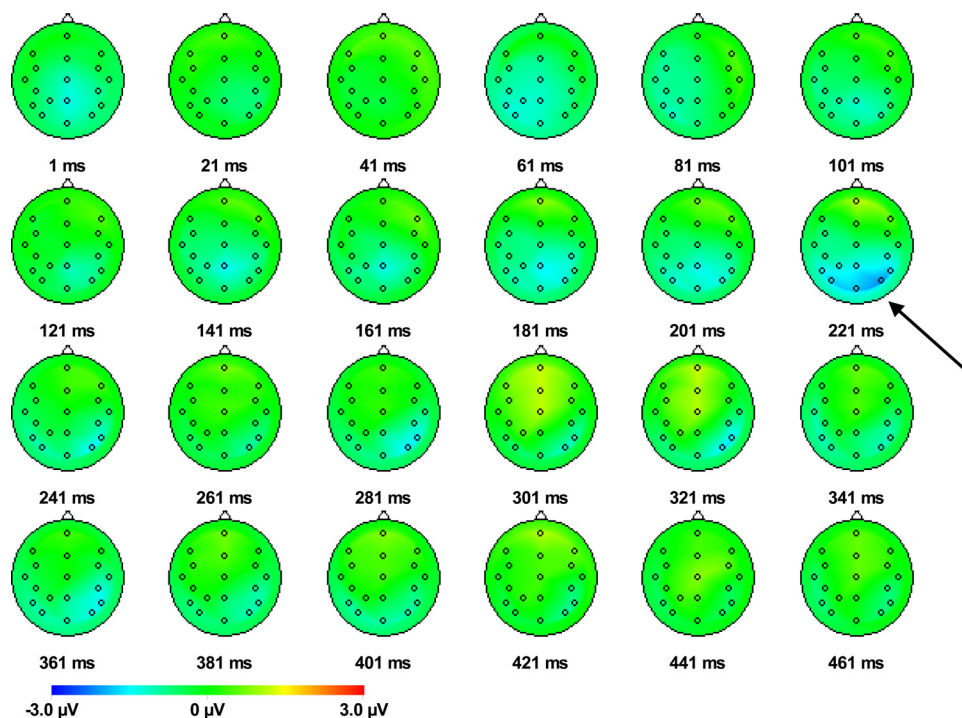


Fig. 5. Effect topography. The effect of rANG TMS is shown across the whole head, computed as rANG – no-TMS on left visual-field, unprimed trials. The arrow marks the time of the onset of statistical significance for the effect.

no-TMS trials, rANG TMS resulted in faster RTs on these switch left visual-field trials when it was delivered during the preceding intertrial interval. As a result of this facilitation of switch trials, priming of pop-out effects for targets in the left hemifield were smaller with rANG TMS. This behavioral effect was mirrored by a negative deflection in ERPs at lateral posterior electrodes that started 210 ms after the onset of the visual search array and was also specific to switch trials with targets in the left visual field. Only rANG TMS produced these parallel behavioral and electrophysiological effects, which were not observed when TMS was applied to either the left or right FEF. The specificity, topography, and time-course of the effects indicate that the rANG is directly involved in the mechanisms that underlie priming of pop-out in visual search—that it performs this role by interacting with visual processing during attentional selection. These effects indicate that attentional reorienting mechanisms are sensitive to implicit memory traces and that the attentional system is updated according to recent trial history during switch trials of priming of pop-out.

A fMRI study of priming of pop-out using a similar task reported that dorsal attentional areas, including parietal cortex, were more active on switch than on repeat trials (Kristjansson et al. 2007). The current TMS study demonstrates that rANG has a critical role on switch but not repeat trials. When rANG TMS was delivered during the intertrial interval, RTs on subsequent switch trials with left visual-field targets were reduced, whereas no such effect was present on repeat trials. It has previously been suggested that slower RTs on switch compared with repeat trials in priming of pop-out experiments are due to interference from an ongoing residual memory trace formed during the previous trial and maintained during the intertrial period (Maljkovic and Nakayama 1994). If the process by which the memory trace updated attentional selection were disrupted during this period (e.g., by rANG TMS), there would be less interference on target discrimination in the following trial, meaning a reduction in the RT cost of switch trials. Our finding of faster responses on switch trials after rANG TMS is therefore consistent with the rANG having a causal role in using task history to update attentional selection. On a switch trial during priming of pop-out, the representation of the target used to guide attention needs to be updated due to the discrepancy between the target color on the current and previous trial. Results from other studies that have applied TMS to the parietal cortex have also been interpreted to show that the parietal cortex has a role in updating representations for attentional selection during a range of other tasks (Rushworth and Taylor 2006), for example, letter detection (Cattaneo et al. 2008). However, parietal areas may be less critical when it is not necessary to update a current representation. For example, the absence of a differential effect of rANG TMS on repeat trials is consistent with previous TMS studies, where rANG TMS did not affect performance in pop-out search tasks under conditions where the color of the pop-out target remained constant across trials so that there were no switch trials (Ashbridge et al. 1997; Ellison et al. 2003).

If rANG TMS had disrupted the memory of target color (independently of attention), effects should have been observed primarily on repeat trials, which was not the case. Whereas it remains theoretically possible that the rANG (or other areas) may be important on primed trials, here, we only found

evidence that the rANG is critical on switch trials, and so, we can only speculate on the mechanisms that may act on primed repeat trials. The difference between primed and switch trials could theoretically be due to two separable processes: facilitation (on repeat, primed trials) and updating for selection (on switch trials, although note that this remains hypothetical given the lack of “neutral” trials in our study). Instead, we suggest the following account of our results. rANG TMS prevents the attentional system from being kept up to date with the latest changes in target color. The rANG is not critical for the memory or for pop-out search per se but rather, for how memory guides attentional search. In priming of pop-out, rANG serves to update the attentional system when the target present on a new trial is incongruent with the memory traces from the previous trial. The attentional mechanisms in control of reorienting after a change in target are themselves sensitive to the memory of the previous trial.

In addition to only modulating target detection performance on switch trials with left visual-field targets, rANG TMS caused a negative ERP deflection at lateral posterior electrodes on exactly these types of trials but not in any other trial condition (this negative deflection could equivalently be considered as a reduction in the amplitude of a positive ERP deflection). This ERP modulation started 210 ms after search-array onset and remained reliably present until at least 240 ms (Fig. 4). This electrophysiological effect provides new evidence from a direct measure of brain activity of how rANG TMS modulates visual pop-out search. This effect emerged at lateral posterior electrodes with a latency of 210 ms, where ERP effects of attention have also been observed in previous studies (Luck and Hillyard 1994), indicating that it reflects a TMS-induced modulation of the higher-order processes through which priming of pop-out affects attentional selection of visual processing on the upcoming trial. This could occur through disrupting how the memory trace of the previous trial affects attentional selection, consistent with the assumption that parietal TMS delivered during the intertrial interval can have an impact on the activation of extrastriate visual areas in response to a subsequently presented search array. Compared with no-TMS trials, rANG TMS resulted in a sustained posterior negativity, which was specific to those trials for which a TMS-induced behavioral facilitation effect was observed. This suggests that this ERP effect reflects the facilitation of visual processing that occurs on those switch trials where rANG TMS reduces the attentional interference associated with residual memory traces of preceding target events. The discrete nature of the effect, lasting from 210 ms to 240 ms, may indicate that the effect of a disruption of the normal effect of this memory trace on attentional selection during priming of pop-out occurs at a highly specific stage in visual processing (and also controls for the possibility of an effect being due to the baseline correction window overlapping with any sustained prestimulus anticipatory potential).

The effect of rANG TMS was strictly confined to the most posterior locations over the occipital lobe (Fig. 5). With the caution necessary when inferring spatial location from ERPs, the topography of the TMS effects suggests that this was an effect of how an attentional guiding or orienting signal from rANG affected visual processing, as opposed to a discrete and limited focal effect on attentional guidance within and limited to the rANG. One interpretation of the sequence of cognitive

operations is then as follows: during the intertrial interval, the implicit memory trace of the previous trial normally updates the attentional selection mechanisms. This process was disrupted by rANG TMS. On switch trials, there is a need for the attentional selection mechanisms to realign the representation of the to-be-attended target after the search array is presented. This occurs via top-down modulation of visual processing in the occipital lobe. rANG TMS disrupts this process and so, causes changes in the occipital ERP on these switch trials. The fact that both behavioral and electrophysiological effects were only present when pop-out targets were presented in the left visual field, that is, contralateral to the stimulated hemisphere, suggests that this modulation of pop-out visual search associated with rANG TMS operates in a spatially selective, hemifield-specific fashion and that rANG is not responsible for top-down control in both hemifields in the same way. Any effect of the rANG in the right visual field was either absent or too weak to be detected, which supports a relative hemispheric asymmetry in the functioning of the rANG. Previous work has suggested that both the left ANG and the rANG may control attention to the right hemifield, while attention to the left hemifield is controlled only by the rANG (Hung et al. 2005; see also Hilgetag et al. 2001 for contralateral effects of parietal TMS that are analogous to the neglect syndrome presented by patients after right parietal damage). This could feasibly also account for the observed hemifield effect on unprimed no-TMS trials, where performance was generally faster for right visual-field than for left-visual stimuli; the left visual field is only controlled by one hemisphere, and less control could mean higher RTs. If participants were near ceiling performance for right visual-field trials (because this visual field receives more control from both hemispheres) then this could theoretically account for the hemifield-specific TMS effects. Note that with either interpretation, the rANG is given a stronger and different role in modulating the right hemisphere (and left visual field) than the left hemisphere (right visual field) during attentional control.

By contrast with the current findings, a previous fMRI study of priming of pop-out reported parietal blood-oxygen level-dependence (BOLD) changes when targets were in either hemifield (Kristjánsson et al. 2007). Differences between that finding and the current study may be driven by the substantial methodological differences between fMRI and ERP: it is possible for a neural change to be evident with either technique and not with the other. Furthermore, although the PPC may show activity that correlates with priming of pop-out in either visual field, our TMS results suggest that it is critical only for the left visual field. The electrophysiological effects of rANG TMS were also unilateral, reaching statistical significance only over the visual cortex of the right hemisphere, in agreement with the contralateral behavioral effects. ERPs can offer a more direct measure of attentional processes than behavioral data alone (e.g., Coles 2003), and this sensitivity may explain why the ERP effects observed here were particularly strong and statistically stronger than the behavioral effects. Other methodological differences—those between TMS and ERP—may explain how TMS enabled observing a context-specific involvement of the stimulated site in the absence of an ERP effect of priming. Combining TMS with ERP allowed revealing the temporally and context-specific involvement of the stimulated site: ERP alone did not show priming effects. The

rANG and other areas may contribute to priming of pop-out at different times in a way in which the ERP method was blind in our study. It is striking that TMS of neither the left nor right FEF had any effect on behavioral or electrophysiological measures of priming of pop-out. This does not necessarily mean, however, that the FEF has no involvement in this task, and future work may yet find effects using different stimulation parameters, such as higher intensities or larger coils (although this might be less compatible with EEG and be less comparable with previous studies). Rather, the lack of an effect in this study with FEF TMS indicates that the effects observed following rANG stimulation cannot be attributed to nonspecific somatosensory or acoustic artifacts accompanying the TMS train in the intertrial interval. Previous work comparing intertrial left or right FEF TMS on priming of pop-out with eye movement responses also found no effects (O'Shea et al. 2007).

Here, we stimulated for a 400-ms time bin during the 2,000-ms intertrial interval, and interactions with other areas outside of the visual cortex could be elicited in future work from stimulation at different times. It may also be important to formalize the necessary intensity for stimulating areas, where no direct output measure (such as the motor-evoked potential for primary motor cortex) currently exists. A neutral condition with intermingled, homogenous, unicolored trials may help determine whether the behavioral effect on no-TMS trials was due more to a facilitation on repeat or inhibition on switch trials. Other effects, possibly including those after FEF TMS, might be demonstrable if the task were made more difficult, the effector were changed, or the consequences of practice were explored.

In summary, the present study found that the rANG plays a causal role during priming of pop-out. TMS of the rANG in the intertrial interval affected behavioral performance and visual activity on trials where the target changed color and was presented on the left, supporting the attentional account of priming of pop-out. The rANG is part of an attentional reorienting mechanism sensitive to the implicit memory of the previous trial and orients attentional selection by interacting ipsilaterally with visual processing.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: P.C.J.T., N.G.M., R.K., V.W., and M.E. conception and design of research; P.C.J.T., N.G.M., and R.K. performed experiments; P.C.J.T., N.G.M., and M.E. analyzed data; P.C.J.T., N.G.M., V.W., and M.E. interpreted results of experiments; P.C.J.T. prepared figures; P.C.J.T. drafted manuscript; P.C.J.T., V.W., and M.E. edited and revised manuscript; P.C.J.T., N.G.M., R.K., V.W., and M.E. approved final version of manuscript.

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